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Use of the Anomeric Allylation Reaction in Natural Products Synthesis - A Stereocontrolled Synthesis of Methyl Deoxypseudomonate B.

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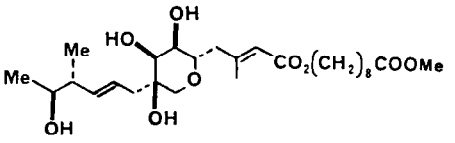
Summary: L-lyxose has been elaborated to methyl deoxypseudomonate B (I) by a sequence of reactions involving the Lewis acid catalyzed anomeric allylation procedure and a stereospecific Grignard addition reaction.

We have reported recently a Lewis acid assisted procedure for effecting the stereoselective allylation of the anomeric site of a glycosyl acetate using allyltrimethylsilane as the nucleophile. In this Letter we further demonstrate the use of this reaction by describing a synthesis of methyl deoxypseudomonate B (I).[2]



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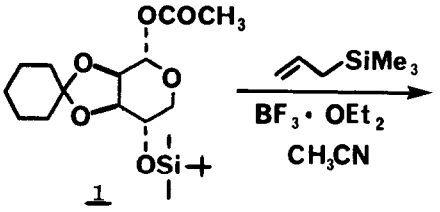
The acetate 1,[3] prepared from L-lyxose, was reacted with allyltrimethylsilane in CH_3CN using $BF_3 \cdot OEt_2$ as catalyst to produce pyrans 2 [$[\alpha]_D^{24}$ -36.9° (c 1.72, $CHCl_3$)] and 3 in a ratio of >80:1 (85% yield). The free hydroxyl group was resilylated (t-Bu(Me)$_2$SiCl, imd., DMAP, DMF), and the olefin subjected to an oxymercuration/demercuration sequence [$Hg(OAc)_2$, camphorsulfonic acid, THF/H_2O; $NaBH_4$][4] to provide the alcohol 4 (3:1 mixture of diastereomers). The newly installed hydroxyl was protected as its benzyloxymethyl ether (ϕCH_2OCH_2Cl, i-Pr_2NEt, CH_2Cl_2) and the silyl group was cleaved (n-$Bu_4N^+F^-$, THF; 85% overall from 4). Oxidation of 5 to the ketone 6 ($CrO_3 \cdot pyr_2$, CH_2Cl_2/Ac_2O; 95%)[5] now enabled us to introduce elements of the lower side chain. The addition of allylmagnesium bromide to this ketone led via a single addition mode to the oily tertiary alcohol 7. The production of solely 7 was anticipated based on an examination of the most stable conformation available to 6 as calculated using the Prophet Computer System.[6] Axial addition is preferred for both steric and electronic reasons (i.e., addition anti to the C-O bond in line with a Felkin-like[7] transition state).[8] Silylation of the tertiary alcohol (t-Bu(Me)$_2$SiOTf, 2,6-lutidine)[8] and Lemieux-Johnson (OsO_4, $NaIO_4$)[9] cleavage of the double bond provided the aldehyde 8 in 87% yield which was coupled in turn with the anion of the optically active sulfone 9.[11] The product of this condensation reaction was isolated as its benzoate, and the isomeric mixture of sulfone-benzoates was cleaved with 5% Na-Hg to produce the desired



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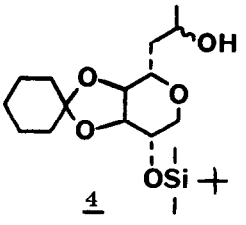

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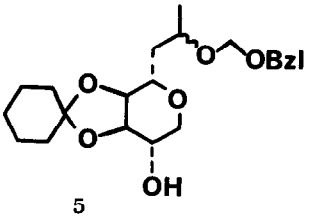

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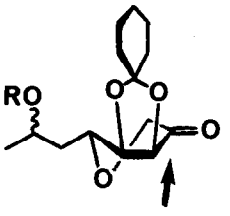

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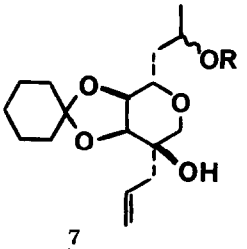

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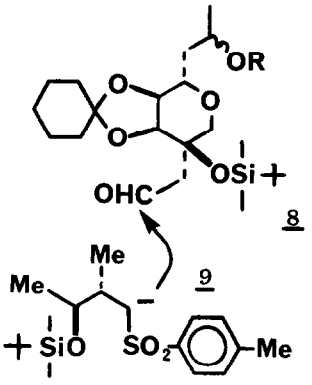

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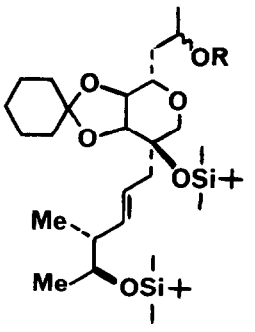

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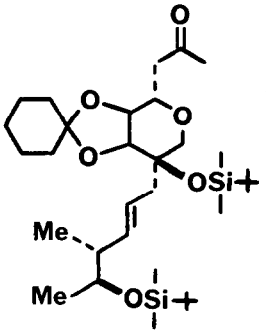
R = CH_2OBzl



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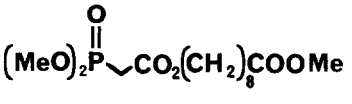

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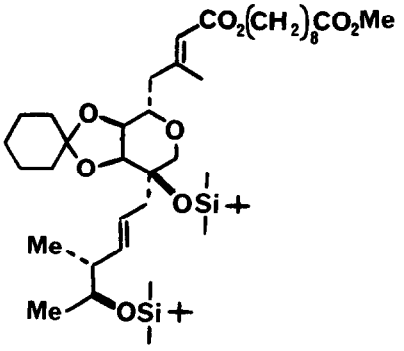

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olefin 10 of E geometry.[12] (C_{10}-H appears as a d of d at δ = 5.43 with J = 15.6, 6.9 Hz; exact mass calcd for $C_{41}H_{72}O_7Si_2$ 732.4817; found 732.4818).

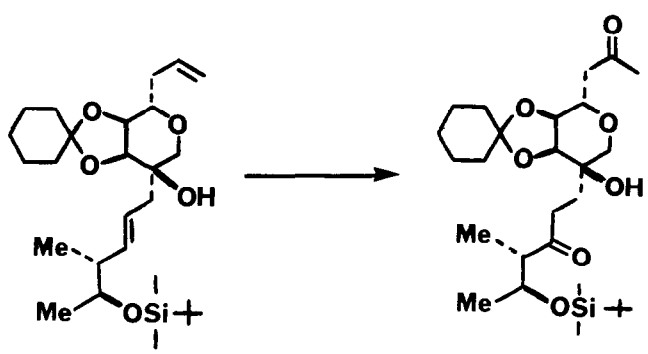
With the lower chain in place, we were now ready to complete the top chain. The benzyloxymethyl group was cleaved (Li, NH_3; 95%) and the alcohol oxidized to ketone using the modified Collins procedure ($CrO_3 \cdot pyr_2$, Ac_2O, 100%).[5] On condensing this ketone with an excess of the sodio derivative of 12,[13] an HPLC separable 4:1-E/Z mixture of esters 13 was formed in 85% yield. The undesired Z ester could be isomerized to a 1:1 mixture of E/Z isomers on irradiation with a sunlamp in an acetonitrile-acetone solution.[14]

The synthesis of the title compound I was completed by removing the silyl groups with $n\text{-}Bu_4N^+F^-$ in THF (3 days) and then the cyclohexylidene ketal with Dowex-50W in MeOH/THF. In the desilylation step, the secondary silyl ether was cleaved at a much faster rate (3 h) than the sterically more encumbered tertiary silyl ether (72 h).

Additional studies are in progress to abbreviate the present synthesis scheme by introducing the lower chain appendage in a single operation.[15,16,17]

References and Notes

1. A. P. Kozikowski, K. L. Sorgi, B. C. Wang, Z.-b. Xu, Tetrahedron Lett., 24, 1563 (1983).
2. For the structural elucidation of pseudomonic acid B, see: E. B. Chain and G. Mellows, J. Chem. Soc., Perkin Trans. I, 318 (1977).
3. Benzyl α-L-lyxopyranoside [E. J. Reist, D. E. Gueffroy and L. Goodman, J. Am. Chem. Soc., 86, 5658 (1964)] was converted to its cyclohexylidene derivative (cyclohexanone, $CuSO_4$, p-TSA, benzene), silylated (t-Bu(Me)$_2$SiCl, imd.), debenzylated (Li, NH_3) and acetylated (Ac_2O, pyr) to provide 1 [mp 42-44.5°C, $[\alpha]_D^{24}$ -13.9° (c 1.23, $CHCl_3$).
4. H. C. Brown and M.-H. Rei, J. Am. Chem. Soc., 91, 5646 (1969). This oxymercuration step became necessary when it was discovered that Wacker oxidation of the diene i led to some of the "over-oxidized" diketone ii.



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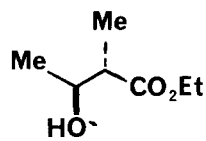
5. P. J. Garegg and B. Samuelsson, Carbohydr. Res., 67, 267 (1978).

6. We thank Mr. Frank Brown of the University of Pittsburgh for carrying out this computation. The Prophet System is sponsored by the Division of Research Resources of NIH.
7. M. Cherest, H. Felkin and N. Prudent, Tetrahedron Lett., 2199 (1968).
8. A similar addition reaction has been reported by Schönenberger and rigorously shown to proceed in the same sense as ours through a ketal equilibration study: B. Schönenberger, W. Summermatter and C. Ganter, Helv. Chim. Acta, 65, 2333 (1982). For an important study on complementary stereoselectivity in the reactions of hexopyranosid-4-uloses with MeMgI and MeLi, see: J. Yoshimura and K. Sato, Carbohydr. Res., 123, 341 (1983).
9. E. J. Corey, H. Cho, C. Rücker and D. H. Hua, Tetrahedron Lett., 3455 (1981).
10. R. Pappo, P. S. Allen, R. U. Lemieux and W. S. Johnson, J. Org. Chem., 21, 478 (1956).
11. The optically active sulfone 9 [$[\alpha]_D^{24}$ +96.1° (c 1.3, $CHCl_3$)] was prepared from the known ester iii [G. Fráter, Helv. Chim. Acta, 62, 2825 (1979)] by a sequence of reactions involving LAH reduction to the diol, selective tosylation of the primary alcohol, t-butyldimethylsilylation of the secondary alcohol, conversion of the tosylate to iodide, and reaction of the iodide with sodium p-toluenesulfinate in DMF.



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12. M. Julia and J.-M. Paris, Tetrahedron Lett., 4833 (1973); P. J. Kocienski, B. Lythgoe and S. Ruston, J. Chem. Soc., Perkin Trans. I, 829 (1978).
13. This phosphonate was conveniently prepared from methyl 9-hydroxynonanoate by treatment with bromoacetyl chloride in pyridine followed by an Arbuzov reaction with trimethylphosphite in refluxing toluene (78%).
14. Spectral data for 13 (E-isomer): IR ($CHCl_3$) 2913, 2824, 1722, 1702, 1644, 1462, 1425, 1355, 1248, 1213, 1155, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (s, 1 H), 5.53 (dt, 1 H, J = 15.8, 6.1 Hz), 5.44 (dd, 1 H, J = 15.8, 6.9 Hz), 4.07 (t, 2 H, J = 6.7 Hz), 4.10 (d, 1 H, J = 4.2 Hz), 3.64-3.74 (m, 2 H), 3.67 (s, 3 H), 3.46 (s, 2 H), 3.36-3.44 (m, 1 H), 2.49 (d, 1 H, J = 14.5 Hz), 2.31 (t, 2 H, J = 7.7 Hz), 2.14-2.46 (m, 4 H), 2.19 (d, 3 H, J = 1.2 Hz), 1.50-1.80 (m, 10 H), 1.20-1.40 (m, 12 H), 1.03 (d, 3 H, J = 6.1 Hz), 0.97 (d, 3 H, J = 6.9 Hz), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.13 (s, 6 H), 0.03 (s, 6 H).
15. Space limitations prevent us from providing spectral data for key intermediates. Details will be provided in the full paper.
16. For other recent completed efforts in the pseudomonic acid area, see: J.-M. Beau, S. Aburaki, J.-R. Pougny and P. Sinaÿ, J. Am. Chem. Soc., 105, 621 (1983); G. W. J. Fleet, M. J. Gough and T. K. M. Shing, Tetrahedron Lett., 24, 3661 (1983).
17. We are indebted to the National Institutes of Health for their support of these studies. Mr. P.-W. Yuen is thanked for his technical assistance.

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